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Genetic parameters of animal traits associated with coccidian and nematode parasite load and growth in Scottish Blackface sheep

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ABSTRACT

Gastrointestinal parasitism is a global problem for grazing ruminants which can be addressed in a sustainable way through breeding animals to be more resistant to disease. This study estimates the genetic parameters of common and new disease phenotypes associated with natural nematode and coccidian infection in Scottish Blackface sheep to underpin future genetic improvement strategies for parasite control. Data on faecal egg counts (**FEC**) from different species of strongyle parasites and faecal oocyst counts (**FOC**) from coccidian parasites were collected on 3-month-old lambs together with a faecal soiling score in the breech area dagginess (**DAG**) and live weight (**LWT**). Faecal count data were obtained for *Strongyles* (**FEC_S**), *Nematodirus* (**FEC_N**) and *Coccidia* (FOC). Data from 3 731 lambs sampled between 2011 and 2017 were included. Faecal egg counts and DAG records were log-transformed prior to analysis. Data were analysed using linear mixed models. Average age at sampling was 92 days with a mean LWT of 24.5 kg. Faecal soiling was not evident in 69% of lambs. *Coccidia* were the most prevalent parasite (99.5%), while Strongyles and *Nematodirus* had a prevalence of 95.4% and 72.7%, respectively. Heritability estimates (±SE) were 0.16 ± 0.03, 0.17 ± 0.03, 0.09 ± 0.03, 0.09 ± 0.03 and 0.33 ± 0.04 for FEC_S, FEC_N, FOC, DAG and LWT, respectively. *Strongyles* faecal egg count had a strong and positive genetic correlation with FEC_N (0.74 ± 0.09) and a moderate positive correlation with FOC (0.39 ± 0.15) while DAG was negatively genetically correlated with LWT (−0.33 ± 0.15). The significant positive genetic correlations between FEC_S, FEC_N and FOC at 3 months of age show that co-selection of sheep for resistance to these different parasites is feasible. Selection for increased resistance to parasite infection is not expected to adversely affect live BW, as no significant antagonistic genetic correlations were found between LWT and FEC. There were significant antagonistic phenotypic and genetic relationships between DAG and LWT being −0.19 ± 0.02 and −0.33 ± 0.15, respectively, indicating that the expression of the manifestation of disease in lambs may be a more meaningful indicator of the impact of parasite burden on productivity.

Implications

Successful implementation of breeding programmes that include disease-related traits described in this paper is a promising method to control important parasites responsible for gastrointestinal parasitic infections affecting sheep. It is a long-term, sustainable alternative to the use of anthelmintics as a way of reducing infection rates, preventing production losses and improving animal efficiency as well as improving animal health and well-being.

Introduction

Animal infection from gastrointestinal (**GI**) parasites constitutes an important contributor to economic losses for sheep production across the world, with those in the United Kingdom estimated on average to be at around £84 million in 2005 (Nieuwhof and Bishop, 2005) with more than 2/3 being due to losses in rate of growth. However, lamb prices have increased since 2005 and financial losses are also likely to have increased. Assuming a 10% reduction in daily weight gain, losses have been at approximately £4.40 per lamb (Wright, 2013). For this reason, GI parasitic infection is a serious constraint in small ruminant production that may greatly reduce the animals productivity levels (Benavides et al., 2015). In sheep, the highest susceptibility to parasite infection is observed in weaned lambs during their first grazing season (Gossner et al., 2012). Lower resistance is observed in young lambs during their first grazing season compared to older sheep, with faecal strongyle egg counts typically peaking at the end of the first grazing season (Stear et al., 1999). This delay in acquisition of immunity may partly reflect age-dependent effects on the anti-parasite immune response as well as parasite-induced immune suppression (McNeilly and Nisbet, 2014).

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The use of anthelmintics is often the favoured choice to control GI nematodes mainly because they are widely available, cost-effective and convenient to use (Venturina, 2012), but the continuous use of these drugs has led to the emergence of resistant strains against the commonly used forms of control (Ellis, 2014; Benavides et al., 2015). The pressure falls on breeders to reduce reliance on the usage of anthelmintics as a means of control (Bishop and Woolliams, 2014). In the United Kindom, the true extent of resistance of pathogens to drugs is difficult to determine as there are no routine surveys being conducted, and generally, resistance is only diagnosed when signs of drug failure are reported (Ellis, 2014).

One viable option to control infection by GI parasites is the development of vaccines as an alternative strategy to anthelmintics, but there has only been a few available vaccines produced to control nematodes (Ellis, 2014). In the case of coccidian parasites, stimulation of development of immunity was successful and achieved using strains that were selected for short but complete life cycles (Vercruysse et al., 2007). There have also been vaccines developed against GI nematodes that originally failed to protect young and susceptible animals (Vercruysse et al., 2007). A vaccine to control *Haemonchus contortus* for calves in Australia (Bassetto et al., 2014) has now been extended for use in sheep Bassetto et al. (2020) and commercialised in Australia as 'Barbervax' and in S. Africa as 'Wirevax'.

Selective breeding programmes have traditionally focussed on the genetic improvement of production traits (Oltenacu and Broom, 2010), which has had a dramatic positive effect on livestock productivity. There is, however, a downside to this improvement, as selection for production traits alone may cause animals to be more susceptible to pathogen infections, with resultant infection-associated production losses (Flori et al., 2011). Indeed, genetic selection focusing on increasing production efficiency was found to restrict the availability of the resources needed for maintenance, reproduction and growth (Rauw, 2012).

The development of breeds selected for resistance to GI parasites appears to be the most promising alternative method to control worm infections (Venturina, 2012). There is evidence of genetic variation among individual sheep in resistance to nematodes, which has been documented in different breeds (Sechi et al., 2009). The genetic control methods to select more resistant individuals relies on the existence of genetic variation (Falconer, 1965) Traditionally, breeding strategies for enhanced resistance to parasites are based on indicator traits like faecal egg counts (**FEC**), for which genetic variation among animals may be manifested even with moderate levels of infection (Zvinorova et al., 2016). Selection of sheep for enhanced resistance to GI parasites is considered feasible under the normal commercial sheep conditions in the United Kingdom in which sheep face natural parasite challenge (Bishop et al., 2004). Nieuwoudt et al. (2002) stated that resistance to GI parasites should be integrated into a broader control programme. The inclusion of GI parasite resistance traits in breeding goals may be of benefit for sheep production enterprises (Bishop et al., 2004). Bishop et al. (2004) also suggested that extra benefit be achieved if the selection is based on both *Strongyles* and *Nematodirus*. Although there has been extensive work investigating the feasibility of selecting sheep for increased resistance to nematodes based on faecal counts, and to a lesser extent, investigating the feasibility of increased resistance to coccidian parasites, there is a clear lack of studies that focus on co-infection between these two distinct classes of parasites.

Nematodes and coccidian parasites are quite different in their morphology and in the way they interact with the host: nematodes are extracellular parasites and are considered to be controlled by Th2 immune responses (McNeilly and Nisbet, 2014), while coccidian parasites infect the host at an intracellular level and generally elicit the development of a Th1 immune response (Engwerda et al., 2014). Stear et al. (2001) raised the possibility of unfavourable consequences for production traits, as well as for other disease traits. In the latter case, there is a concern that increasing resistance to one disease may result in increased susceptibility to another disease. This is important due to the possible antagonism between Th1 and Th2 responses. However, this relationship between these types of immunity, commonly referred to as Th1/Th2 dichotomy has not been successfully proven in sheep (McRae et al., 2014), with the involvement of immunoregulatory genes in animals infected by nematodes further putting into question the existence of such dichotomy (Hassan et al., 2011).

For that reason, the objective of the present study was to estimate genetic parameters of parasitic infection indicator traits. Heritability estimates of faecal counts of different parasitic genera/species were derived to assess the feasibility of genetic selection for enhanced resistance. Heritability of faecal soiling (dagginess (**DAG**) score), which is indicative of GI pathology, and live weight (**LWT**) as a measure of productivity were also estimated, and genetic correlations between parasitic infection indicator traits and DAG scores and LWT were also estimated to determine what impact selection for parasite resistance would have on pathology and production.

Material and methods

Animals

A total of 3 731 Scottish Blackface sheep lambs were sampled from 2011 to 2017 (Table 1) and did not receive anthelmintic treatment prior to sampling. The animals belonged to the SRUC experimental Castlelaw hill farm flock in the Pentland hills, Midlothian, Scotland. Lambs were managed under typical hill farm conditions and were exposed to natural infection. Animals were allocated at random to different grazing locations associated with their heft (home range) which resulted in their sire not being confounded with grazing area. The description of the genetic line is detailed in Lambe et al. (2008). In short, the flock was split into three selection lines of animals as 'Selection' (S), Control (C) and Industry (I). The S and C lines were selected using the selection index as described by Conington et al. (2001) as being high- or average-performing, respectively. The I line was selected on visual appearance only with no regard to performance data.

Traits and measurements

Data collection was performed when animals were approximately 3 months of age (August in 2011; July from 2012 to 2017). Separate faecal count measurements were obtained for *Strongyles* (FEC_S), *Nematodirus* (FEC_N) and *Coccidia* (**FOC**) using the McMaster technique (Whitlock, 1948) and were analysed in eight different SRUC labs. Additionally, LWT were measured and dagginess (DAG) (faecal soiling scores), characterized by an accumulation of faecal matter around the perineum were evaluated visually at the time of FEC sampling, using a 5-point scale (0–4), where 0 means no evidence of faeces, and 4 means a significant accumulation of faeces.

Data analysis

Preliminary analyses determined the fixed effects affecting each of the studied traits (Table 2). Subsequently, using ASREML (Gilmour et al., 2009a), mixed models were used to obtain trait heritability (h^2) estimates in univariate analyses, and genetic (r_g) and phenotypic (r_p) correlations between traits in bivariate analyses. All analyses were based on the following model:

Table 1
Number of lambs sampled per year.

	Years						
	2011	2012	2013	2014	2015	2016	2017
Animals	548	548	512	493	554	640	436

Table 2
Statistically significant fixed effects in the model for lamb traits.

Traits	Fixed effects
FEC_S	sx, lab, fec_age, yr, brrnk, mk_graz, yr.brrnk, yr.mk_graz, brrnk.mk_graz, yr.lab
FEC_N	sx, lab, fec_age, yr, brrnk, mk_graz, yr.brrnk, yr.mk_graz, yr.lab
FOC	sx, lab, fec_age, yr, brrnk, mk_graz, yr.brrnk, yr.mk_graz, yr.lab
DAG	sx, yr, brrnk, mk_graz, yr.mk_graz, brrnk.mk_graz
LWT	sx, dage, line, yr, brrnk, fec_age, mk_graz, yr.brrnk, yr.mk_graz, brrnk.mk_graz

Abbreviations: FEC_S = strongyle faecal egg count; FEC_N = Nematodirus faecal egg count; FOC = Coccidiosis faecal egg count; DAG = dag score; LWT = live weight; sx = sex of lamb (2 levels, entire male and female); lab = laboratory (8 levels); fec_age = age at sampling; yr = year of faecal sampling 7 levels 2011–2017; brrnk = birth-rearing rank (10 levels), mk_graz = grazing location (12 levels); dage = age of dam; line = genetic line; "." is used to indicate an interaction.

$$Y = X\beta + Za + e$$

where

- Y = the studied trait (FEC_S, FEC_N, FOC, DAG and LWT) record
- β = vector of statistically significant fixed effects
- a = vector of additive genetic effects including animal pedigree
- e = vector of random residual effects
- X and Z = design matrices relating records to fixed or random effects.

Statistically significant fixed effects, summarized in Table 2 by trait, include sex of the animal, grazing location at marking age (approximately 2 months of age), birth-rearing rank, year of birth, lab where faeces were analysed, genetic line and age of dam at parturition. Age of lambs at the time of sampling was fitted as a covariate.

Data for FECs, FEC_N, FOC and DAG had 1 added to each value and log-transformed prior to analysis to get the distributions closer to normality. Analyses were conducted with ASReml v3.0 (Gilmour et al., 2009a) within the statistical package R.

Results

Table 3 summarises descriptive statistics for all studied traits. *Coccidia* were the most prevalent parasite infecting nearly all lambs (99.5%), followed by *Strongyles* found in 95.4% of lambs and *Nematodirus* with 72.7% of animals having eggs in faeces. The fixed effects showed some interesting trends as male lambs had significantly higher levels of FEC_S and FEC_N (by 0.225 and 0.198 s.d., respectively), tended to have higher FOC and DAG, and were 926 g heavier than female lambs. Compared to lambs born and raised as being single, twin born and raised lambs had 0.119 s.d. higher FECs and 0.123 s.d. higher for FEC_N and were 2.65 kg lighter. Twin born and raised lambs also tended to have higher levels of all worm species compared to twin lambs raised as a single lamb; the latter category was still lighter by 376 g compared to single born and raised lambs. Compared to the base of 2011, the year of birth effect (7 levels) ranged between −0.014 and 0.19 s.d. for FECs, −1.09 to 0.35 s.d. for FEC_N, −0.55 to 0.58 for FOC, −0.79 to 0 s.d. for DAG, and −3.054 to 0.425 Kg for LWT. Similarly, the range of s.d. differences for grazing location (12 levels) compared to the base was −0.055 to 0.77, −0.43 to 0.31 and −0.59 to 0.20 s.d. difference for FECs, FEC_N and FOC, respectively. The age of lamb at the time of measurement for all worm species was important. For every unit increase (day) in age, FECs, FEC_N and FOC declined by 0.014, 0.015 and 0.011 s.d., respectively, with the daily LWT gain being 178 g.

Trait h^2 and genetic and phenotypic correlations between traits are shown in Table 4. All h^2 estimates were significantly greater than zero ($P < 0.05$). Faecal count estimates differed between parasite genera. Disease trait h^2 (FEC_S, FEC_N, FOC and DAG) were low, varying from 0.09 to 0.17. LWT h^2 was moderate (0.33 ± 0.04). There was a strong positive r_g between FEC_S and FEC_N (0.74 ± 0.09) and a moderate r_g between FEC_S and FOC (0.39 ± 0.15). We also found a moderate negative r_g between LWT and DAG (−0.33 ± 0.15). Phenotypic correlations were generally weaker than their genetic counterparts. All three parasites were found to have weak but significant correlations between them, varying from 0.09 ± 0.02 and 0.23 ± 0.02. Both nematodes were equally correlated with LWT (−0.06 ± 0.02). LWT and FOC were negatively correlated with DAG (−0.19 ± 0.02 and −0.06 ± 0.02, respectively).

Table 3
Descriptive statistics and variance component estimates for each lamb trait.

	Number of animals	Mean (eggs/g)	CV (%)	Range
FEC_S	3 731	714.66	136	0–37500
FEC_N	3 731	226.57	142	0–2800
FOC	3 731	30 631.82	152	0–1053000
DAG (score)	3 183	0.38	245	0–4
LWT (kg)	3 725	24.49	17	14–42.1

Abbreviations: FEC_S = strongyle faecal egg count; FEC_N = Nematodirus faecal egg count; FOC = Coccidiosis faecal egg count; DAG = dag score; LWT = live weight.

Discussion

The present study aimed to assess the genetic background of traits related to GI parasitic infection in Scottish Blackface sheep, as well as assessing the relationships between disease traits and productivity. To that end, genetic parameters on faecal counts on three major parasite genera, namely, *Strongyles*, *Nematodirus* and Coccidia, were derived along with genetic parameters on DAG scores and LWT. Results revealed significant and heritable genetic variation among animals for all these traits.

Our FEC_S h^2 estimates are in line with those of the Appeninica Italian breed, but our FOC estimate is somewhat lower (Filippini et al., 2006). Heritability for FEC_N falls within the range of McManus et al. (2009) while oocyst counts h^2 estimates were also lower than those in their multi-breed experiment in Brazil. Nematode h^2 estimates (FEC_S and FEC_N) were broadly similar to results for a New Zealand study using the information on more than 2 million pedigreed animals that include records on sheep breeder and research flocks (Pickering et al., 2012).

Table 4
Genetic parameters for faecal counts (FEC_S, FEC_N and FOC), dag scores (DAG) and live weights (LWT) in lambs.

Traits	FEC_S (SE)	FEC_N (SE)	FOC (SE)	DAG (SE)	LWT (SE)
FEC_S	0.16 (0.03)[1]	0.23 (0.02)[1]	0.13 (0.02)[1]	0.02 (0.02)	−0.06 (0.02)[1]
FEC_N	0.74 (0.09)[1]	0.17 (0.03)[1]	0.09 (0.02)[1]	0.00 (0.02)	−0.06 (0.02)[1]
FOC	0.39 (0.15)[1]	0.23 (0.16)	0.09 (0.03)	−0.06 (0.02)[1]	0.02 (0.02)
DAG	0.06 (0.18)	0.02 (0.18)	0.03 (0.21)	0.09 (0.03)[1]	−0.19 (0.02)[1]
LWT	−0.01 (0.13)	−0.08 (0.12)	0.25 (0.15)	−0.33 (0.15)[1]	0.33 (0.04)[1]

Abbreviations: FEC_S = strongyle faecal egg count; FEC_N = Nematodirus faecal egg count; FOC = Coccidiosis faecal egg count.
Phenotypic (r_p) and genetic (r_g) correlations are presented above and below the diagonal (heritability), respectively.
[1] Estimates are significantly different from zero ($P < 0.05$).

Moderate h^2 estimates of nematode FEC have been found in Merino lambs raised in Brazil (Benavides et al., 2016), in Texel sheep in the United Kingdom (Bishop et al., 2004) and in back-cross lambs derived from purebred populations of Martinique Black Belly and Romane (Assenza et al., 2014). Nematode FEC h^2 of 0.29 was estimated for Scottish Blackface sheep by Bishop and Stear et al. (1999) at 6 months of age, but lower estimates have been reported for the same breed (0.14 to 0.22) (Bishop et al., 1996). According to Bishop (2012), most egg count h^2 for egg excretion in sheep generally falls within a range of 0.20 to 0.40. Although outside of this range, our estimates for nematode FEC are not far from the lower limit of this interval. Estimates of FOC h^2 are in line with results for goats (Rout et al., 2015; Sharma et al., 2017). In contrast, Reeg et al. (2005) studying Merinoland lambs, found remarkably high estimates beyond 2 months of age (0.54 to 0.79). While it may not be advisable to select Merino sheep for resistance at younger ages than 2 months, there is evidence to suggest that there are strong influences, at a genetic level, on oocyst excretion in older lambs.

Although significant, our DAG h^2 estimate was low compared to previous estimates in other sheep breeds (Bisset et al., 1992; Pickering et al., 2012). One explanation for this could be that, in our data, approximately 70% of lambs showed no signs of soiling around the breech area, while only 4% had a DAG score of 3 or higher. It is possible that the level of parasite challenge was lower in this study and/or the sheep used in this study generated a less severe inflammatory response to the parasites. LWT heritability estimates obtained here are in line with previous reports on the same and other sheep breeds (McEwan et al., 1992; Bishop et al., 1996; Safari et al., 2005; Benavides et al., 2016).

We found strong genetic correlations between FEC_S and FEC_N, revealing that FEC_S and FEC_N are largely under the same genetic control. Our results are well within the range of previous estimates (Bisset et al., 1992; McEwan et al., 1992; Amarante et al., 2004; Bishop et al., 2004; Morris et al., 2004; Wolf et al., 2008; Pickering et al., 2012). Correlated responses in resistance to *Nematodirus* are expected when selecting for low FEC_S. To the best of authors' knowledge, there are few studies involving both nematode parasites and Coccidia. In our study, we found that at 3 months of age FEC_S and FOC are moderately and positively correlated, suggesting these two parasites are partially under the same genetic control and that there is no antagonistic relationship between these parasites. Consistently negative r_G between FEC_S and FOC were found previously in Appenninica sheep breed (Filippini et al., 2006). In a Brazilian study involving different sheep breeds no meaningful r_G between these parasites was reported (McManus et al., 2009). Differences with results previously reported may be attributed to different lamb age and breed populations. Using Spearman's rank correlation tests, Craig et al. (2008) found positive associations between *Strongyles* and *Coccidia* in yearling and adult St. Kilda Soay sheep, although they state this may simply be a result of similar responses to the host condition or due to co-variation in parasite intake. Nevertheless, the same authors highlight the importance of genetic studies to produce h^2 estimates as well as correlations between different parasites, possibly allowing for a balanced selection. In Nellore cattle, a strong correlation between nematodes and coccidian parasites was found across a range of ages, which could indicate the possibility of genes regulating immune defence having pleiotropic effects that alter resistance to different parasites in the same direction, or alternatively, linked genes could be responsible for the defence mechanisms (Passafaro et al., 2015).

No meaningful r_g between FEC traits and LWT was found. From a genetic selection standpoint, such results are favourable; this suggests that selection for increased resistance will not adversely affect animal production and growth. The impact of parasitism on lamb LWT have been a point of contention in the literature where unfavourable (McEwan et al., 1992; Morris et al., 2005; Pickering et al., 2012) as well as favourable genetic correlations between nematode FEC and LWT have been previously reported (Eady, 1998; Gauly et al., 2004). There is also evidence that the correlation may shift from strongly positive at low FEC to negative at high FEC levels (Rashidi et al., 2014). With studies yielding such a wide range of genetic correlations between these traits, it is hard to generalize, as there are multiple factors that might contribute to differing results including variation in breeds, parasite genera and species, the intensity of the infection, method of statistical analysis, treatment protocols, and selection history.

In addition to the lack of antagonism between resistance to parasitic infection and productivity (LWT) found in the present study, we emphasize on the clear favourable (negative) genetic correlation between DAG and LWT. DAG is an indicator of diarrhoea, which in young lambs is assumed to be caused by GI parasites. The significance of dag scores associated with increased risk of flystrike was highlighted by Greeff et al. (2014). That study estimated the heritability of dag scores at different ages and genetic correlations with flystrike in the breech area of the sheep with a view to it being an indicator trait that could potentially be used to breed indirectly for resistance to breech strike. Although the correlations between dag and worm egg counts were not reported in that study, strong, significant genetic correlations (0.64 to 0.81) were estimated between dag and flystrike in the breech area rendering it a very useful indicator trait to breed breech strike resistant sheep in a Mediterranean environment. In the United Kingdom, farmers have to crutch (remove wool) the breech area prior to lambs being sent for slaughter to remove any faecal soiling therefore faecal soiling is a trait of economic importance. Additionally, recent evidence (Zhao et al., 2019) showed that animals selected for low FEC were subject to what is termed 'hypersensitivity-associated diarrhoea' resulting in higher soiling of the breech area (dags) compared to unselected controls. While the current study found weak correlations between dag score and parasite faecal counts, they agree with those of Brown et al. (2010) which were also reported to be very low and not significantly different from zero. These conclusions suggest that selection to improve resistance to GI parasitism in sheep would not necessarily lead to a reduction in faecal soiling therefore dag score also should be included in breeding programmes. The interactions among immunological parameters and disease should be explored further as cited by Zhao et al. (2019) and indeed are currently the subject of further study with the same animal population reported in this study. In addition, in a study of New Zealand sheep, the genetic correlations between DAG and nematode egg counts have been reported to be negative at 3 months but positive at 8 months of age (Pickering et al., 2012) which further complicates the messages around this issue. Genetic correlations between dag scores and faecal counts were not significant in the present study perhaps due to the low number of instances of DAG scores higher than 0 in our population, although there was a tendency for there to be a positive genetic correlation of DAG with FEC_S and FEC_N. A significant positive correlation between FEC and DAG was also reported in Romney sheep (Bisset et al., 1992). A negative correlation between DAG and LWT in this study indicates that lower DAG scores are associated with higher lamb LWT, which will have a positive impact on productivity; this was also reported in the study of Brown et al. (2010).

In conclusion, our study reveals that nematode and coccidian counts in Scottish Blackface lamb faeces are lowly heritable, but there is significant genetic variation among individuals to underpin a selective breeding programme aiming to enhance animal resistance to infection. Our results suggest that there is a consistently strong genetic correlation between the two species of nematodes, implying that selecting to reducing output for one will also affect the other. Furthermore, there is no evidence of antagonism between nematode FEC and FOC. These results are encouraging because the implementation of a breeding programme focusing on these traits will result in animals with greater overall resistance. The inclusion of these traits in a breeding programme will allow the development of a selection index.

Ethics approval

The animals used in this study were subject to approvals by the SRUC Animals Experiments Committee (AEC). The flock operates

under license granted by the UK Home Office Animals Scientific Procedures Act 1986.

Data and model availability statement

The genetic model used for the analyses was not deposited in an official repository. Data on animal performance, pedigree and health traits are maintained in a secure SQL database at SRUC and are available upon request from the corresponding author.

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Antonio Pacheco: Formal analysis. Writing – original draft. Tom McNeilly: Writing – review & editing. Funding acquisition. Supervision. Joanne Conington: Funding acquisition. Conceptualisation. Data curation. Methodology. Writing – review & editing. Supervision. Georgios Banos: Funding acquisition. Methodology. Software. Writing – review & editing. Supervision.

Declaration of interest

None.

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